

ABVD as the Treatment Option in Advanced Hodgkin's Lymphoma Patients Older than 45 Years

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Abstract Advanced age is considered an unfavourable prognostic factor for Hodgkin's lymphoma (HL). The optimal treatment for these patients is not yet defined, especially for the advanced stages. We analysed the outcome and prognostic relevance of patient and disease characteristics in 46 advanced stage HL patients who were older than 45 years, treated with ABVD. Elderly patients (>60 year) had a significantly higher rate of comorbidities ($p < 0.05$). The complete remission rate was significantly lower in elderly patients and in patients with an IPS ≥ 3 ($p < 0.05$, $p < 0.05$, respectively). Elderly patients had significantly shorter event-free survival ($p < 0.01$) and overall survival ($p < 0.01$) compared to patients of 45–60 year. Extranodal disease, an IPS ≥ 3 , bulky disease, an ESR > 50 and the presence of a large mediastinal tumour mass didn't have an influence on survival ($p > 0.05$). The multivariate Cox regression analysis identified the age of >60 year as an independent prognostic factor. The prospective clinical trials seem to be needed for defining the optimal therapeutic approach in elderly patients.

Keywords Advanced Hodgkin's lymphoma · Elderly patients

Introduction

The prognosis of Hodgkin's lymphoma (HL) has been constantly improving over the last few decades [1]. The advances in the risk stratification of patients on diagnosis and the risk adopted optimization of therapy are having a major effect on this [2]. However, the prognosis of elderly patients with HL still remains unsatisfactory [3].

In the past few years, many prognostic scores have been developed to identify patients with a high risk of a poor outcome. Several studies identified advanced age as an unfavourable prognostic factor for HL [4–8]. The International Prognostic Score (IPS), the most commonly used prognostic score for HL, identified the age at the time of diagnosis (more than 45) as an unfavourable risk factor [9]. The age limit varies in different studies, ranging from more than 45 up to more than 65 [9,10].

Few factors have been proposed as possible underlying reasons for a poor outcome in these patients. A high percentage of accompanying comorbidities, low compliance and the high percentage of toxic events in conventional treatment are considered the age related reasons for a poor outcome [11–18]. Several studies identified that the biology of the disease is distinct and more aggressive in elderly patients compared to young patients, with a higher rate of mixed cellularity subtype classical HL (cHL), infradiaphragmatic presentation and advanced stage [4,5,11–16]. The discrepancy between these factors, mainly the biology of the disease and the high toxicity of the aggressive approach that is required for these patients, still remains the great obstacle for defining the optimal therapeutic approach for elderly patients, especially in advanced stages.

In this study, we analysed the outcome in advanced HL patients older than 45 years treated with ABVD chemotherapy. These patients have age as one of the risk factors

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according to the IPS [9]. Patients younger than 45 years were not included in the study since this population does not have the high percentage of comorbidity that is supposed to be one of the reasons for a poor outcome in elderly patients. Also, we analysed the impact on the complete response rate and survival of IPS score, the presence of comorbidity, extranodal disease, a large mediastinal tumour, “bulky” disease and ESR > 50 mm/h. All the analyses were performed on the whole group of patients, organized into two subgroups that were created based on age from 45 to 60 years and more than 60 years, since the treatment of refractory/relapsed disease in these two groups was different.

Patients and Methods

Case Selection

This retrospective analysis was performed on 46 advanced stage HL patients (CS II B with a large mediastinal tumour mass or extranodal disease, CS III and IV) older than 45 years, who were diagnosed and treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy at the Clinic for Hematology, Clinical Center of Serbia between June 1997 and June 2007. In all cases, the diagnosis of classical Hodgkin lymphoma was confirmed by immunophenotyping and classified according to the World Health Organization (WHO) classification of tumours of hematopoietic and lymphoid tissues in the Laboratory of Hematopathology, Clinic for Hematology, Clinical Center of Serbia. All the patients were assessed for cardiac function by cardiac ultrasound before receiving ABVD. The other organ function assessment was performed if the patient had a history of some disease or if the symptoms, physical or laboratory findings were suggestive of organ impairment. None of the patients who received ABVD had diagnosed cardiac failure or hypokinetic cardiac segment. Six patients who had some of the above mentioned abnormalities on the cardiac ultrasound were treated with COPP (cyclophosphamide, vincristine, procarbazine, prednisone) instead. Two more patients with seriously disabling concomitant diseases (ECOG performance status > 1) were treated in the same way, one with unstable angina pectoris and one with chronic obstructive lung disease. Also, patients who were previously treated for another malignancy were not included in this study.

Medical records were reviewed to determine the gender, IPS, presence of B symptoms, bulky disease (a diameter of tumour > 7 cm), a large mediastinal tumour mass (involves more than 1/3 of the chest diameter on the chest x-ray), extranodal localisation, ESR > 50 mm/h, treatment response and survival.

Treatment Recommendations

All patients were treated according to the institutional standard of care at the time of diagnosis. The patients who responded after four cycles of ABVD proceeded with ABVD therapy to complete VI to VIII cycles, depending on the treatment response (complete or partial remission) and treatment tolerance. After completing ABVD, the patients received additional radiation therapy (RT) on the sites of tumour involvement. Patients with a refractory disease or a relapse after initial chemotherapy received salvage chemotherapy with the DHAP regimen (dexamethasone, cisplatin, Ara-c) if they were 45–60 years old, while patients older than 60 years received COPP.

Statistical Methods

Overall survival (OS) was measured from the date of diagnosis until the date of death from any cause, or the last follow up visit. Event-free survival (EFS) was measured

Table 1 Baseline characteristics of analyzed patients ($n=46$)

Age, years	
Mean	53.5 (range 45–80)
45–60	36 (78.3%)
>60	10 (21.7%)
Co-morbidity	
Total	27 (58.7%)
45–60	18 (50%)
>60	9 (90%)
Stage	
IIB	6 (13%)
III	20 (43.5%)
IV	20 (43.5%)
Systemic symptoms	41 (89%)
Histology	
LP	1 (2.2%)
NS	25 (54.3%)
MC	14 (30.4%)
LD	2 (4.4%)
Unclassified	4 (8.7%)
Extranodal involvement	
No	17 (37%)
Yes	29 (63%)
Bulky disease	
No	29 (63.1%)
Medistinum bulky	13 (28.2%)
Other bulky	4 (8.7%)
IPS score	
0–2	14 (30.4%)
3+	32 (69.6%)

Table 2 Adherence to initial treatment plan, toxicity and complete remission rate according to age

Age, years	45–60	>60	<i>P</i>
Total	36 (78.3%)	10 (21.7%)	
Completed chemotherapy	31 (86.1%)	4 (40%)	<i>F</i> (<i>p</i>)=0.006
Toxicity related deaths	0	2 (20%)	
CR	27 (75%)	2 (20%)	<i>F</i> (<i>p</i>)=0.003

from the date of diagnosis to that of disease progression or death from any cause or to the last follow up visit.

The association between the patient’s/disease characteristics and treatment response was determined using the chi-square (X^2) and Fisher’s exact tests (*F*).

Survival functions were estimated using the Kaplan-Meier method and compared using the log-rank test.

A multivariate analysis was performed to evaluate the potential predictive value of the disease and patient characteristics as a risk factor.

Results

The median follow up was 37 months, from 2 to 93 months. The median age of the patients was 53.5 years (range 45–80). Ten patients (21.7%) were older than 60 year. Comorbidities were present in 27 patients (58.7%). In patients older than 60 year, a significantly higher rate of comorbidities (90% vs. 50%, *F*=0.031) was recorded. The most frequent concomitant disease was arterial hypertension, present in 24 out of 27 patients (88.9%). The other conditions that were present are diabetes mellitus, angina pectoris, rheumatoid arthritis, chronic obstructive lung disease, duodenal ulcer, meningioma and Crohn’s disease. The baseline characteristics on diagnosis are summarized in Table 1.

Table 3 Complete remission rate according to disease characteristics

Characteristic	CR	<i>P</i>
IPS score		
0–2	12 (86%)	<i>F</i> (<i>p</i>)=0.035
3+	17 (53%)	
Large mediastinal tumor		
No	20 (61%)	<i>p</i> >0.05
Yes	9 (69%)	
Bulky disease		
No	18 (62%)	<i>p</i> >0.05
Yes	11 (65%)	
Extranodal disease		
No	10 (58%)	<i>p</i> >0.05
Yes	19 (66%)	
ESR>50		
No	7 (78%)	<i>p</i> >0.05
Yes	22 (60%)	

A total of 35 patients (76.1%) completed the planned chemotherapy schedule, of which 31 proceeded to radiotherapy, while four patients underwent second line chemotherapy. Twenty-nine patients (63%) achieved complete remission, with a significantly lower rate in patients older than 60 year (20% vs. 75%, *F*=0.003).

In the group of patients older than 60 years, 4 (out of 10) patients completed the planned chemotherapy. Three patients died within 6 months of establishing diagnosis, 1 in febrile neutropenia, 1 from cardiac failure and 1 from disease progression. Three patients started second line treatment before completing the planned treatment schedule due to resistant disease. In eight patients older than 60 years (80%), grade 3–4 neutropenia was recorded.

In the group of patients aged 45–60 years, one patient died due to progressive disease. In one patient, the treatment was abandoned due to toxicity (prolonged neutropenia). Due to resistant disease, three patients started second line treatment before completing the planned treatment schedule.

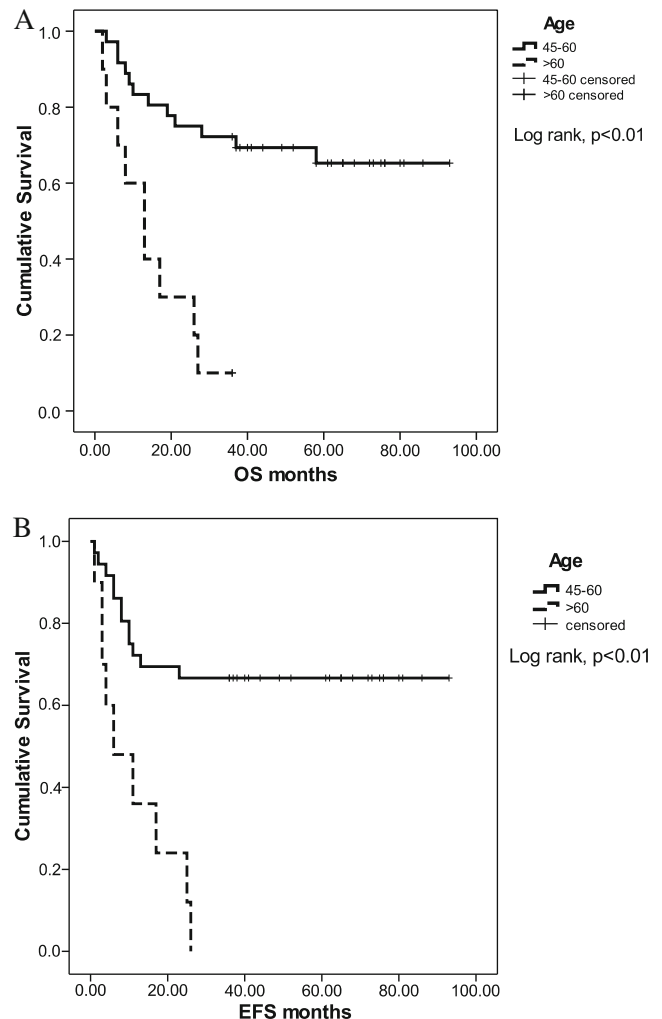


Fig. 1 Survival in group of 46 advanced stage HL according to the age: **a.** Overall survival **b.** Event free survival

The information on completing the initial therapeutic plan and treatment response according to age is summarized in Table 2.

There was a significant difference in CR rate regarding the IPS. Patients with an IPS > 3 had a statistically significant lower CR rate compared to patients with an IPS 0–2 (53% vs. 86%, $F=0.035$). The same result was recorded in both observed age groups. There was no difference in achieving complete remission regarding the presence of a large mediastinal tumour (61% vs. 69%, $F=0.424$), extranodal disease (58% vs. 66%, $\chi^2=0.65$, $p>0.05$), bulky disease (62% vs. 65%, $\chi^2=0.858$, $p>0.05$) or an ESR > 50 mm/h (78% vs. 60%, $F=0.268$). Furthermore, a difference was not observed between the age groups. The differences in achieving CR depending on disease characteristics are summarized in Table 3.

Survival analysis revealed that patients older than 60 years had highly significant shorter event-free survival (log rank 14.798, $p=0.000$) and overall survival compared to patients of 45–60 year (log rank 16.593, $p=0.000$) (Fig. 1).

The patients who had an IPS ≥ 3 , extranodal disease, bulky disease or an ESR > 50 mm/h had shorter event-free and overall survival but statistical significance was not reached (Fig. 2). There was no difference in survival depending on the presence of a large mediastinal tumour mass at the presentation.

In the multivariate analysis, we included the baseline characteristics of the patients and the disease and only an age of > 60 years was identified as an independent prognostic factor for a poor outcome.

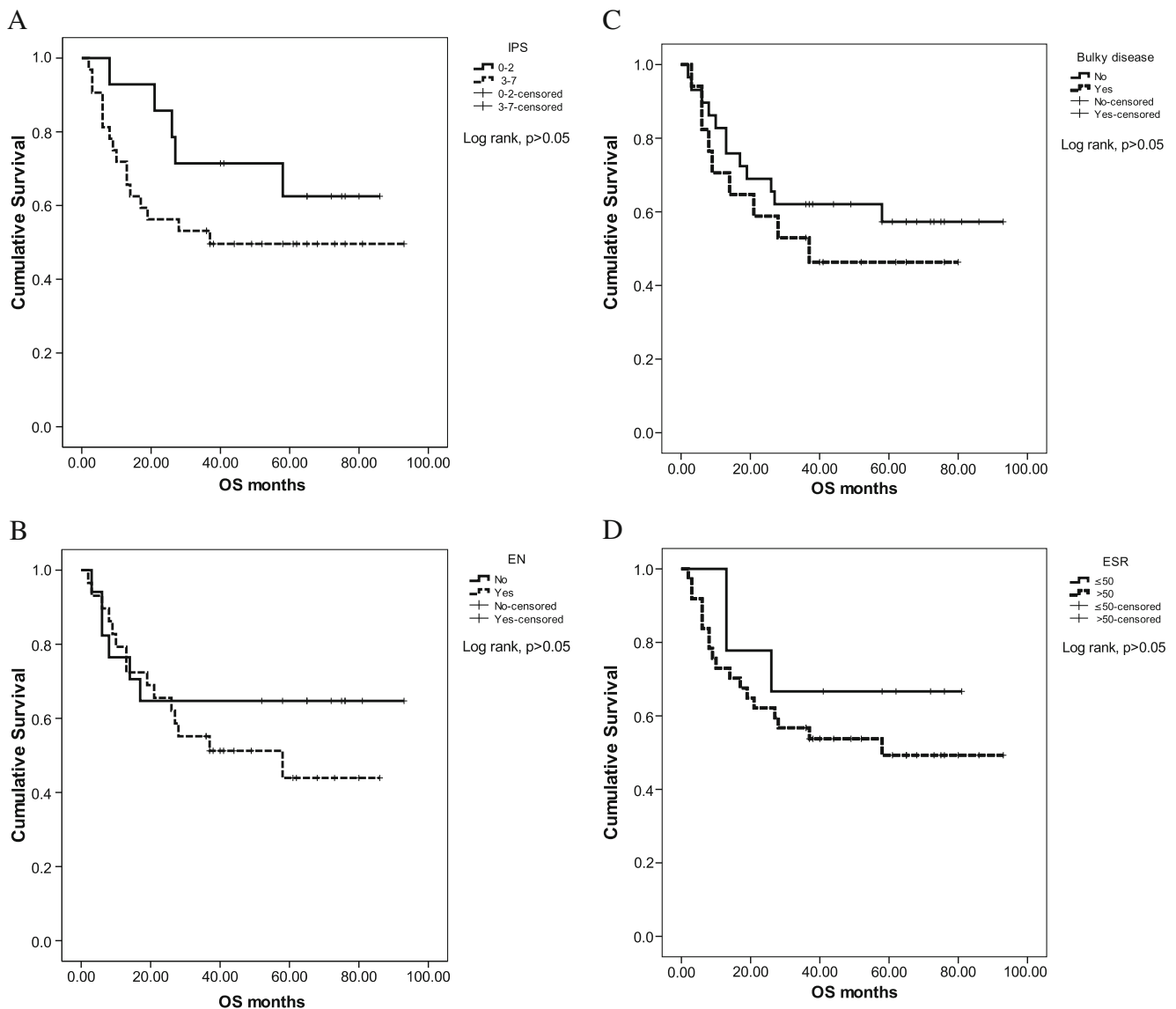


Fig. 2 Overall survival according to disease characteristics. **a** IPS score; **b** Extranodal disease; **c** Bulky disease; **d** ESR

Discussion

The main goal in treating elderly patients with HL is to achieve CR since many authors agree that elderly patients who achieved CR with conventional treatment experience the same relapse-free survival (RFS) as younger patients [7, 13–16]. However, conventional treatment can't be applied in many elderly patients because of age-related comorbidities and poor performance status [15,16]. Even if the patients are in good condition, elderly people are vulnerable to chemotherapy and the risk of toxic events is a major problem [13,15,19].

Attempts at treating elderly patients with low dose regimens were successful in reducing toxicity but the results were not encouraging [19,20]. The CVP/CEP regimen induced a high rate of CR, but a discouraging high relapse rate was recorded in the follow-up period [19]. The Stanford's VBM regimen proposed for early stages HL was well tolerated by elderly patients but obtained a CR rate in stage III and IV that was very low, only 33% [20]. More favourable results were achieved with the recent reduced intensity regimen VEPEMB, especially in advanced stage patient, with a 58% CR rate and 34% 5-year failure-free survival [10].

In this study, we analysed the outcome of advanced stage HL patients where age was a risk factor according to Hasenclever's study [9], who were treated with the ABVD regimen followed by radiotherapy. For the purpose of analysis, we compared the outcome in elderly patients with the adjacent age group, who also have age as a risk factor according to the IPS score (45–60 years). Also, the treatment for relapsed/refractory disease was different. The results of treatment were completely diverse, even though all the patients in this study were assessed as having a good condition and adequate organ function regardless of the age before starting chemotherapy. The results obtained in the group of patients older than 60 years were poor, with only 20% of them achieving CR, with a high toxicity rate and a high percentage of early deaths (30%). A high rate of severe toxicities and treatment-related deaths in elderly patients are also reported by other authors [4,13,16,21]. In the group of patients aged 45–60 years CR rate was 75%, with a low percentage of toxicity and early deaths. These results are similar to the results from other authors [22–28]. The presence of comorbidity was indicated in many publications as one of the main reasons for the discrepancy in the outcome between younger and elderly patients [15,16]. In our group of patients, we recorded a significant difference in the presence of comorbidity regarding age. However, according to our experience, the presence of comorbidity itself is not sufficient to explain the huge discrepancies in the outcome between the two groups examined. A possible answer might lie in the fact that the most common comorbidities in the

elderly population are systemic chronic diseases, such as hypertension and diabetes mellitus, which can cause multi-organ damage not detectable with conventional diagnostic methods. This hypothesis should be confirmed on a larger series of patients.

The analysis of the prognostic factors revealed that an age of more than 60 years is an independent prognostic factor for a poor outcome.

The importance of an aggressive approach even in the elderly was shown in the Nebraska Lymphoma study group comparison of the effects of ChIVPP and ChIVPP/ABV. The results of this study suggest that the inclusion of doxorubicin should be the most important component of HL treatment in the elderly [29]. Escalated BEACOPP, the new intensive regimen that became widely accepted for advanced stages of HL, in spite of its higher toxicity compared to conventional therapy, brought major improvements in the outcome of HL patients [30]. However, in elderly patients, even treatment with the less aggressive baseline BEACOPP resulted in significantly higher toxicity with no benefit in FFTF or overall survival compared to conventional treatment [31]. Encouraging results were recorded in studies that investigated aggressive chemotherapy combined with the reduction of radiotherapy, in both young and elderly HL patients [15,32,33]. Recent researches demonstrated promising therapeutic effects and good tolerance of lenalidomide in patients with refractory and multiple relapsed Hodgkin lymphoma [34]. Based on these observations, an international phase I/II study of lenalidomide combined with conventional chemotherapy (AVD-Rev) for elderly HL patients has been initiated [34].

In order to define the best treatment strategy for elderly advanced stage HL patients, new prospective studies that include a better pre-treatment evaluation of patients and the reduction of radiotherapy seem to be needed.

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